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α-synuclein and cytosolic dopamine: Stabilizing a bad situation

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The intriguing finding that α-synuclein—a protein recently found to be mutated in some familial cases of Parkinson disease—and cytosolic dopamine interact to form adducts that stabilize a presumably toxic intermediate of fibril formation provides clues into the mechanism of neurodegeneration.

Parkinson disease (PD) is a neurodegenerative disorder characterized by resting tremor, rigidity, and difficulty in initiating voluntary movement. These deficits are primarily due to the progressive death of neuromelanin-expressing dopamine (DA) neurons of the substantia nigra. The pathological hallmarks of PD are Lewy bodies; large non-membrane-bound inclusions composed of ubiquitinated and aggregated protein fibrils, which are absent in normal substantia nigra DA neurons.

Most PD cases are 'idiopathic'; that is, with no known genetic or environmental cause. However, mutations in at least three proteins underlie rare instances of autosomal PD. The first mutation to be discovered in PD patients was in a presynaptic protein, α-synuclein (α-SYN)[1]. In the 9 November issue of *Science*[2], Lansbury and colleagues suggest that DA and α-SYN might interact to initiate the specific neurodegeneration of substantia nigra neurons in familial and idiopathic PD. The interaction appears to produce a DA–α-SYN adduct that stabilizes a presumably toxic intermediate, the so-called **protofibril**, by inhibiting its conversion to fibrils.

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α-SYN is a natively unfolded protein, but contains an A2 apolipoprotein α-helix-like region—a region that is suspected to reversibly bind vesicular membranes[3]. The findings that α-SYN knockout mice show an enhanced rate of recovery of DA synaptic transmission[4], whereas inhibition of α-SYN expression in culture reduces the population of synaptic vesicles in the 'reserve pool'[5], suggests that α-SYN functionally interacts with synaptic vesicles, perhaps by modulating vesicle trafficking. It is not yet clear how these apparently normal actions of α-SYN might relate to PD etiology.

A clue that mutant α-SYN may provide a toxic gain of function came from the discovery that α-SYN is a major component of the insoluble fibrils of Lewy bodies in PD, and possibly in amyloid plaques in Alzheimer disease[6]. The transformation of α-SYN from a soluble state to mass aggregated fibrils involves an increase in β-sheet content and progressive oligomerization. Transient small units of oligomers of β-folded proteins are known as protofibrils. The two known α-SYN mutations that underlie autosomal PD enhance the rate of **protofibril** formation[7], whereas oligomerization of α-SYN with the closely related protein β-SYN inhibits fibrillization[8].

In an effort to identify drugs that interfere with α-SYN fibrillization, Conway *et al.*[2] tested many different commercially available compounds. Notably, the compounds found to block fibril formation were catecholamines, including DA and its precursor, L-DOPA. The block occurred during the process of oligomerization, by stabilizing the **protofibril** at the expense of fibril formation. Catecholamines are readily oxidized in the presence of iron to highly reactive metabolites, such as DA-quinone (DAQ), that covalently bind

metabolites, such as DA-quinone (DAQ), that covalently bind proteins. Because antioxidants that maintain DA in a reduced state also block its inhibition of fibril formation, it is likely that the DAQ metabolite plays a role in **protofibril** stabilization.

Conway *et al.* then reacted α-SYN with DA and isolated DAQ–α-SYN adducts. The native α-SYN and DAQ–α-SYN adduct were mixed at varying ratios to compare the rate of fibrillization. A low fraction of DAQ–α-SYN inhibited conversion of protofibrils to fibrils—in other words, DAQ may actually inhibit Lewy body formation by binding α-SYN.

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A number of cellular mechanisms keep DA from associating with α-SYN and causing neurotoxicity. Several of these involve keeping cellular levels of DAQ below a certain threshold. Neurotoxicity due to elevated cytosolic DA and resulting DAQ formation has long been implicated in neurodegeneration from models of methamphetamine toxicity[9]. When cytosolic DA exceeds the native antioxidative buffering of the neuronal cytosol, DAQ and associated oxyradicals are produced. Cytosolic DA is normally maintained at a safe level via uptake into synaptic vesicles, release from the cytoplasm by reversal of the DA uptake transporter, and breakdown by monoamine oxidase. If DAQ is still produced, it can be sequestered by glutathione.

If, despite these protective mechanisms, DAQ remains and succeeds in modifying soluble cytosolic proteins such as α-SYN, the ubiquitin–proteasome pathway can degrade the damaged proteins. Parkin, a protein that in mutant form underlies rare cases of autosomal PD, may be required for α-SYN degradation by the ubiquitin–proteasome pathway[10]. Another protective mechanism could be by autophagy of cytosolic DAQ modified proteins, which results in accumulation of neuromelanin in substantia nigra during normal aging.

Perhaps these pathways are sufficient to inhibit PD in most individuals. However, for those for whom it is not, fibrillation and Lewy body formation may be a last resort for removing DAQ damaged α-SYN (Fig. 1). If this is true, the Lewy body will be thought of in a new light: as a desperate attempt by the neuron to save itself by sequestering protofibrils.

It is striking that substantia nigra neurons can display enormous Lewy bodies that occupy most of the perikariya, in addition to neuromelanin granules that occupy much of the remaining cytosol. If Lewy bodies were protective, the finding would be consistent with recent reports in other

neurodegenerative disorders, including Huntington disease and spinocerebellar ataxia, where ubiquitinated fibrillar aggregates appear to be protective. In this light, it is interesting that the autosomal recessive PD linked to *parkin* mutations lacks Lewy bodies—an observation consistent with protofibrils, and not fibrils, being the toxic agents.

A requirement for cytosolic catecholamines in **protofibril** stabilization would provide an explanation of why most PD cell death occurs in substantia nigra and neuromelanin-expressing norepinephrinergic neurons of the locus coeruleus. Similarly, if α-SYN inhibits **protofibril** formation, a α-SYN deficiency may explain why Lewy bodies are formed in non-catecholaminergic neurons in a related disorder, Diffuse Lewy Body disease[8].

A caveat in these models is that experiments on α-SYN **protofibril** formation have been conducted in cell-free systems. Clearly, additional cytosolic factors such as glutathione, ubiquitination and autophagy will modify these pathways in the substantia nigra. It will be interesting to see if mice with mutant α-SYN exposed to chemical models of PD neurodegeneration such as 6-hydroxy-dopamine, which readily produces DAQ, or MPTP, show results consistent with this model. It is also imperative to establish why protofibrils are neurotoxic. Given the possible functional association of α-SYN with synaptic vesicles, perhaps protofibrils perturb intracellular membranes; indeed the Lansbury group has noted a disruption of synthetic vescicles by protofibrils[11]. If DA synaptic vesicle membrane is damaged, protofibrils could further increase cytosolic DA levels.

As promising as these newly identified mechanisms are, they do not solve the central riddle of why some individuals develop idiopathic PD. However, the unification of two previously separate areas of investigation, cytosolic DA and α-SYN pathogenic mechanisms, has provided some intriguing clues that may help unravel this enigma.

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